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#1	Search **oncogene[jour] AND 5[volume] AND 587 [page]** Field: **Title Word**	11:55:10	0

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☐ 1: Cancer Res 1999 Jun 1;59(11):2566-9

Related Articles, Links

Discovery and initial characterization of the paullones, a novel class of small-molecule inhibitors of cyclin-dependent kinases.

Zaharevitz DW, Gussio R, Leost M, Senderowicz AM, Lahusen T, Kunick C, Meijer L, Sausville EA.

Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, Maryland 20892-7444, USA. zaharevitz@dtpax2.ncifcrf.gov

Analysis of the National Cancer Institute Human Tumor Cell Line Anti-Cancer Drug Screen data using the COMPARE algorithm to detect similarities in the pattern of compound action to flavopiridol, a known inhibitor of cyclin-dependent kinases (CDKs), has suggested several possible novel CDK inhibitors. 9-Bromo-7,12-dihydro-indolo[3,2-d][1] benzazepin-6(5H)-one, NSC-664704 (kenpaullone), is reported here to be a potent inhibitor of CDK1/cyclin B (IC50, 0.4 microM). This compound also inhibited CDK2/cyclin A (IC50, 0.68 microM), CDK2/cyclin E (IC50, 7.5 microM), and CDK5/p25 (IC50, 0.85 microM) but had much less effect on other kinases; only c-src (IC50, 15 microM), casein kinase 2 (IC50, 20 microM), erk 1 (IC50, 20 microM), and erk 2 (IC50, 9 microM) were inhibited with IC50s less than 35 microM. Kenpaullone acts by competitive inhibition of ATP binding. Molecular modeling indicates that kenpaullone can bind in the ATP binding site of CDK2 with residue contacts similar to those observed in the crystal structures of other CDK2-bound inhibitors. Analogues of kenpaullone, in particular 10-bromopaullone (NSC-672234), also inhibited various protein kinases including CDKs. Cells exposed to kenpaullone and 10-bromopaullone display delayed cell cycle progression. Kenpaullone represents a novel chemotype for compounds that preferentially inhibit CDKs.

PMID: 10363974 [PubMed - indexed for MEDLINE]

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i686-pc-linux-gnu Oct 3 2002 17:23:10

File 155:MEDLINE(R) 1966-2002/Oct W2
***File 155: Alert feature enhanced for multiple files, duplicates** removal, customized scheduling. See HELP ALERT.

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      Set  Items  Description
      ---  -----  -----------
?s p16 and cdk4
            3277  P16
            1456  CDK4
      S1     472  P16 AND CDK4
?s s1 not py=>1999
             472  S1
         1823538  PY=>1999
      S2     227  S1 NOT PY=>1999
?s s2 and fahraeus
             227  S2
              98  FAHRAEUS
      S3       0  S2 AND FAHRAEUS
?s s2 and c(w)myc
             227  S2
          734268  C
           13961  MYC
           10431  C(W)MYC
      S4       3  S2 AND C(W)MYC
?t/full/1
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4/9/1
DIALOG(R)File 155:MEDLINE(R)

10036484 99027595 PMID: 9811456
Investigation of the cell cycle regulation of cdk3-associated kinase activity and the role of cdk3 in proliferation and transformation.
Braun K; Holzl G; Soucek T; Geisen C; Moroy T; Hengstschlager M
Obstetrics and Gynecology, University of Vienna, Department of Prenatal Diagnosis and Therapy, Austria.
Oncogene (ENGLAND) Oct 29 1998, 17 (17) p2259-69, ISSN 0950-9232 Journal Code: 8711562
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
The G1-S transition in mammalian cells has been demonstrated to require the cyclin-dependent kinases cdk2, cdk3 and **cdk4** /6. Here we show that a novel kinase activity associated with cdk3 fluctuates throughout the cell cycle differently from the expression of cyclin D1-, E- and A-associated kinase activities. Cdk3 kinase activity is neither affected by **p16** (in contrast to **cdk4** /6) nor by E2F-1 (in contrast to cdk2), but is downregulated upon transient p27 expression. We found cdk3 to bind to p21 and p27. We provide evidence that p27 could be involved in the regulation of the cell cycle fluctuation of cdk3 activity: cdk3 protein does not fluctuate and interaction of cdk3 with p27, but not with p21, is lost when cdk3 kinase becomes active during the cell cycle. In Myc-overexpressing cells, but not in normal Ratl cells, constitutive ectopic expression of cdk3 induces specific upregulation of cdk3-associated kinase activity that is still cell cycle phase dependent. Ectopic cdk3, but not cdk2, enhances Myc-induced proliferation and anchorage-independent growth associated with Myc activation, without effects on cyclin D1, E and A protein expression or kinase activities. High levels of cdk3 in Myc-overexpressing cells trigger up- and deregulation of E2F-dependent transcription without inducing the E2F-DNA binding capacity. In contrast to all other studied positive G regulators, cdk3 is unable to cooperate with ras in fibroblast transformation suggesting a function of cdk3 in G1 progression that is different from cyclin D- or E-associated kinase activities. Our data provide first insights into the regulation of cdk3-associated kinase activity and suggest a model how cdk3 participates in the regulation of the G1-S transition.

4/9/2
DIALOG(R)File 155:MEDLINE(R)

10017545 98447600 PMID: 9774342

A novel function of adenovirus E1A is required to overcome growth arrest by the CDK2 inhibitor p27(Kip1).

Alevizopoulos K; Catarin B; Vlach J; Amati B
Swiss Institute for Experimental Cancer Research (ISREC), CH-1066 Epalinges, Switzerland.

EMBO journal (ENGLAND) Oct 15 1998, 17 (20) p5987-97, ISSN 0261-4189 Journal Code: 8208664
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS

We show here that the adenovirus E1A oncoprotein prevents growth arrest by the CDK2 inhibitor p27(Kip1) (p27) in rodent fibroblasts. However, E1A neither binds p27 nor prevents inhibition of CDK2 complexes in vivo. In contrast, the amount of free p27 available to inhibit cyclin E/CDK2 is increased in E1A-expressing cells, owing to reduced expression of cyclins D1 and D3. Moreover, E1A allows cell proliferation in the presence of supraphysiological p27 levels, while **c - Myc** , known to induce a cellular p27-inhibitory activity, is only effective against physiological p27 concentrations. E1A also bypasses G1 arrest by roscovitine, a chemical inhibitor of CDK2. Altogether, these findings imply that E1A can act downstream of p27 and CDK2. Retinoblastoma (pRb)-family proteins are known CDK substrates; as expected, association of E1A with these proteins (but not with p300/CBP) is required for E1A to prevent growth arrest by either p27 or the **CDK4** /6 inhibitor **p16** (INK4a). Bypassing CDK2 inhibition requires an additional function of E1A: the mutant E1A Delta26-35 does not overcome p27-induced arrest, while it binds pRb-family proteins, prevents **p16** -induced arrest, and alleviates pRb-mediated repression of E2F-1 transcriptional activity (although E1A Delta26-35 fails to restore expression of E2F-regulated genes in p27-arrested cells). We propose that besides the pRb family, E1A targets specific effector(s) of CDK2 in G1-S control.

09/780,566

WEST Search History

DATE: Tuesday, October 15, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,JPAB,EPAB; THES=ASSIGNEE; PLUR=YES; OP=ADJ			
L9	L8 and cdk4	0	L9
L8	overexpress c-myc	21	L8
L7	L6 and screen agent	0	L7
L6	L1 and neuroblastoma	52	L6
L5	L1 amd Burkitt lympboma	0	L5
L4	L2 and screen compound	3	L4
L3	L2 and screen agents	5	L3
L2	L1 and c-myc	53	L2
L1	cdk4	248	L1

END OF SEARCH HISTORY

L4: Entry 1 of 3 File: USPT Oct 31, 2000

US-PAT-NO: 6140052
DOCUMENT-IDENTIFIER: US 6140052 A

TITLE: cMYC is regulated by Tcf-4

DATE-ISSUED: October 31, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
He; Tong-Chuan	Chicago	IL		
Vogelstein; Bert	Baltimore	MD		
Kinzler; Kenneth W.	BelAir	MD		

US-CL-CURRENT: 435/6; 435/325, 435/366

CLAIMS:

We claim:

1. A method of determining the presence or absence in a cell of wild-type Adenomatous polyposis coli (APC) or a wild-type downstream protein in the APC transcription regulatory pathway, comprising the steps of:

introducing a Tcf-responsive reporter gene into the cell, wherein the Tcf-responsive reporter gene comprises a Tcf-binding element of c-MYC; and

measuring transcription of said reporter gene; wherein a cell which supports active transcription of said reporter gene does not have wild-type APC or a downstream protein in the APC transcription regulatory

pathway.

2. The method of claim 1 wherein the Tcf-responsive reporter gene comprises a Tcf binding element selected from the group consisting of TBE1 (CTTTGAT), TBE2 (ATCAAAG), and combinations thereof.

3. The method of claim 1 wherein the Tcf-responsive reporter gene comprises nucleotides -1194 to -484 of c-MYC (SEQ ID NO:14).

4. The method of claim 1 wherein the Tcf-responsive reporter gene comprises nucleotides -1194 to -741 of c-MYC (SEQ ID NO:14).

5. The method of claim 1 wherein the Tcf-responsive reporter gene comprises nucleotides -741 to -484 of c-MYC (SEQ ID NO:14).

6. A method of determining the presence or absence in a cell of wild-type APC, comprising the steps of:

contacting a Tcf-responsive reporter gene with a lysate of the cell, wherein the Tcf-responsive reporter gene comprises a Tcf-binding element of c-MYC; and

measuring transcription of said reporter gene; wherein a lysate which inhibits

said transcription has wild-type APC.

7. The method of claim 6 wherein the Tcf-responsive reporter gene comprises a Tcf binding element selected from the group consisting of TBE1 (CTTTGAT), TBE2 (ATCAAAG), and combinations thereof.

8. The method of claim 6 wherein the Tcf-responsive reporter gene comprises nucleotides -1194 to -484 of c-MYC (SEQ ID NO:14).

9. The method of claim 6 wherein the Tcf-responsive reporter gene comprises nucleotides -1194 to -741 of c-MYC (SEQ ID NO:14).

10. The method of claim 6 wherein the Tcf-responsive reporter gene comprises nucleotides -741 to -484 of c-MYC (SEQ ID NO:14).

11. A method of identifying candidate drugs for use in Familial Adenomatous Polyposis (FAP) patients, patients with APC or .beta.-catenin mutations, or patients with increased risk of developing colorectal cancer, comprising the steps of:

contacting a cell having a Tcf-responsive reporter gene and having no wild-type APC or a mutant .beta.-catenin with a test compound, wherein the Tcf-responsive reporter gene comprises a Tcf-binding element of c-MYC;

measuring transcription of a Tcf-responsive reporter gene, wherein a test compound which inhibits the transcription of the reporter gene is a candidate drug for colorectal cancer therapy.

12. The method of claim 11 wherein the Tcf-responsive reporter gene comprises a Tcf binding element selected from the group consisting of TBE1 (CTTTGAT), TBE2 (ATCAAAG), and combinations thereof.

13. The method of claim 11 wherein the Tcf-responsive reporter gene comprises nucleotides -1194 to -484 of c-MYC (SEQ ID NO:14).

14. The method of claim 11 wherein the Tcf-responsive reporter gene comprises nucleotides -1194 to -741 of c-MYC (SEQ ID NO:14).

15. The method of claim 11 wherein the Tcf-responsive reporter gene comprises nucleotides -741 to -484 of c-MYC (SEQ ID NO:14).

16. The method of claim 11 wherein the cell produces an APC protein defective in .beta.-catenin binding or regulation.

17. The method of claim 11 wherein the cell produces a .beta.-catenin protein which is super-active, or which is defective in APC binding or resistant to APC regulation.

18. The method of claim 11 wherein the cell produces no detectable APC protein.

19. A method of identifying candidate drugs for use in FAP patients, patients with APC or .beta.-catenin mutations, or patients with increased risk of developing colorectal cancer, comprising the steps of:

contacting a Tcf-responsive reporter gene which comprises a Tcf-binding element of c-MYC with a test compound under conditions in which the reporter gene is transcribed in the absence of the test compound; and

measuring transcription of the Tcf-responsive reporter gene; wherein a test compound which inhibits said transcription is a candidate drug for colorectal cancer therapy.

20. The method of claim 19 wherein the Tcf-responsive reporter gene comprises a Tcf binding element selected from the group consisting of TBE1 (CTTTGAT), TBE2 (ATCAAAG), and combinations thereof.

21. The method of claim 19 wherein the Tcf-responsive reporter gene comprises nucleotides -1194 to -484 of c-MYC (SEQ ID NO:14).

22. The method of claim 19 wherein the Tcf-responsive reporter gene comprises nucleotides -1194 to -741 of c-MYC (SEQ ID NO:14).

23. The method of claim 19 wherein the Tcf-responsive reporter gene comprises nucleotides -741 to -484 of c-MYC (SEQ ID NO:14).

24. The method of claim 19 wherein the step of contacting is performed in the presence of a lysate of a cell which has no wild-type APC.

25. The method of claim 19 wherein the step of contacting is performed in the presence of a lysate of a cell which has a mutant .beta.-catenin defective in APC binding or resistant to APC regulation or which is super-active.

26. The method of claim 24 wherein the cell produces an APC protein defective in .beta.-catenin binding or regulation.